

## Rejuvenation of the muscle stem cell population restores strength to injured aged muscles.

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### Public Summary:

The elderly often suffer from progressive muscle weakness and regenerative failure. We demonstrate that muscle regeneration is impaired with aging owing in part to a cell-autonomous functional decline in skeletal muscle stem cells (MuSCs). Two-thirds of MuSCs from aged mice are intrinsically defective relative to MuSCs from young mice, with reduced capacity to repair myofibers and repopulate the stem cell reservoir in vivo following transplantation. This deficiency is correlated with a higher incidence of cells that express senescence markers and is due to elevated activity of the p38alpha and p38beta mitogen-activated kinase pathway. We show that these limitations cannot be overcome by transplantation into the microenvironment of young recipient muscles. In contrast, subjecting the MuSC population from aged mice to transient inhibition of p38alpha and p38beta in conjunction with culture on soft hydrogel substrates rapidly expands the residual functional MuSC population from aged mice, rejuvenating its potential for regeneration and serial transplantation as well as strengthening of damaged muscles of aged mice. These findings reveal a synergy between biophysical and biochemical cues that provides a paradigm for a localized autologous muscle stem cell therapy for the elderly.

### Scientific Abstract:

The elderly often suffer from progressive muscle weakness and regenerative failure. We demonstrate that muscle regeneration is impaired with aging owing in part to a cell-autonomous functional decline in skeletal muscle stem cells (MuSCs). Two-thirds of MuSCs from aged mice are intrinsically defective relative to MuSCs from young mice, with reduced capacity to repair myofibers and repopulate the stem cell reservoir in vivo following transplantation. This deficiency is correlated with a higher incidence of cells that express senescence markers and is due to elevated activity of the p38alpha and p38beta mitogen-activated kinase pathway. We show that these limitations cannot be overcome by transplantation into the microenvironment of young recipient muscles. In contrast, subjecting the MuSC population from aged mice to transient inhibition of p38alpha and p38beta in conjunction with culture on soft hydrogel substrates rapidly expands the residual functional MuSC population from aged mice, rejuvenating its potential for regeneration and serial transplantation as well as strengthening of damaged muscles of aged mice. These findings reveal a synergy between biophysical and biochemical cues that provides a paradigm for a localized autologous muscle stem cell therapy for the elderly.

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